The Examiner has rejected claims 1-18 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner has rejected claims 1-18 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Contag, et al., (U.S. Patent No. 5,650,135, hereinafter referred to as '135) and Georgiou, et al., in view of Kasahara, et al.

These rejections are believed to be overcome in part by the amendments and are otherwise traversed for reasons discussed below.

Overview of the Amendments

Claims 1, 2-7, 10, 11, 12, and 18 have been amended without prejudice or disclaimer. Amendment of these claims is not intended to be an acquiescence in the Office's assessment of those claims in the 5 December 2000 Communication, and applicants expressly reserve the right to bring the subject matter of the original claims again in a subsequent, related application.

Basis for the amendment of claim 1 can be found throughout the specification, for example, at least at the following locations: page 7, lines 3-7; page 20, line 24, to page 21, line 5; and page 22, line 1, to page 23, line 23.

Claims 2, 3, 4, 5, 6, 7, 10, 12 and 18 have been amended to provide appropriate antecedent basis for the terms used therein.

Basis for the amendment of claim 11 can be found throughout the specification, for example, at least at the following location: page 19, lines 18-26.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested.

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Addressing the Examiner's Rejections

1. Objection to Claim 1.

The Examiner has objected to claim 1 because the claim did not end in a period. Applicants thank the Examiner for noting this informality. The informality is corrected by amendment in this paper.

Accordingly, the applicants respectfully request withdrawal of the objection.

2. Rejection of Claims 1-18 under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-18 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner has asserted the following specific deficiencies in the claims.

A. Claim 1

The Examiner asserts that recitation of "recognition" and the phrase "causes expression of the reporter gene to generate a reporter gene product" are vague and indefinite.

In order to facilitate prosecution, applicants have (i) limited moiety recognition to the binding of the substance to the ligand-binding domain; and, (ii) clarified the last section of the claim to recite that expression of the reporter gene, mediated by the transcription control element, causes expression of a reporter gene product that provides a detectable signal. For example, when the reporter gene encodes a luciferase, light is produced (i.e., the detectable signal) in the presence of an energy source, oxygen, and a substrate (see, for example, specification page 24, lines 12-24).

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B. Claim 4

The Examiner has objected to use of the phrase "reporter gene product is bioluminescence" asserting that use of the phrase renders the claim vague and indefinite.

In order to facilitate prosecution, applicants have amended the claim to clarify antecedent basis relative to claim 3, on which claim 4 depends.

C. Claim 5

The Examiner has objected to use of the term "luciferase" asserting that use of the term renders the claim vague and indefinite.

In order to facilitate prosecution, applicants have amended the claim to provide correct antecedent basis and to recite that the reporter gene encodes a luciferase.

D. Claim 7

The Examiner has objected to use of the term "element" asserting that use of the term has insufficient antecedent basis.

Applicants have amended the claim to conform claim 7 with the language of claim 1, from which claim 7 depends.

E. Claim 11

The Examiner has objected to use of the phrase "or fragment thereof" asserting that use of the term renders the claim vague and indefinite.

The limitations of originally presented claim 11 have been incorporated into independent claim 1. Applicants have amended the original language of claim 11 to recite that the fragments have the immunological property of epitope binding.

Applicants thank the Examiner for the Examiner's careful attention to the language of the claims. In view of the above amendments, the teachings of the

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specification and the level of ordinary skill in the present art, the applicants submit that the claims are clear and definite and that the boundaries of the claims are capable of being understood by one of ordinary skill in the art. Applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph.

3. Rejection of Claims 1-18 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-18 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Contag, et al., ('135) and Georgiou, et al., in view of Kasahara, et al.

For all of the following references, distinctions between the recited limitations in claim 1 and each cited reference are pointed out. Claim 1 is the only independent claim; all other pending claims ultimately depend from claim 1. Accordingly, all of the dependent claims distinguish over the references at least by virtue of their recitation of the limitations presented in independent claim 1.

The PTO has the burden of establishing a case of *prima facie* obviousness, and can meet this burden "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 5 USPQd2 1596 (Fed. Cir. 1988). No such objective teaching has been presented concerning the biodetectors of the present invention. The Examiner has provided no reference that answers the question of why one of ordinary skill in the art would chose to generate the combination of the present invention.

The reference of Contag, et al., teaches, for example, *in situ* activatable promoter-controlled expression of a bioluminescent protein in cells of a transgenic animal stimulated by a promoter inducer, e.g. interferon-activated promoter stimulated by infection with a virus ('135, col. 3, lines 13-17). However, the reference does not teach or suggest biodetectors constructed according to the teachings of the present invention. For example, the reference of Contag, et al., does not teach or suggest a signal converting

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element, comprising (i) an extracellular ligand-specific binding domain which specifically binds the selected substance, wherein the ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain, wherein binding of target substance to the epitope-binding fragment of the ligand-specific binding domain activates the intracellular signal transforming domain, thus providing an activated intracellular signal transforming domain (amended claim 1).

The reference of Georgiou, et al., does not make up for the shortcomings of the reference of Contag, et al. The reference of Georgiou, et al., teaches only (i) the display of foreign proteins and peptides on the surface of a number of micro-organisms and (ii) screening for the presence of such foreign proteins and peptides on the surface of the microorganism. The reference teaches use of FACs to identify surface expression of such foreign proteins. The reference also teaches use of such surface display for the production of live, recombinant bacterial vaccines. The reference does not contain any teaching or suggestion of the biodetectors of the present invention. For example, the reference does not teach or suggest a signal converting element, comprising (i) an extracellular ligand-specific binding domain which specifically binds the selected substance, wherein the ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain, wherein binding of target substance to the epitope-binding fragment of the ligand-specific binding domain activates the intracellular signal transforming domain, thus providing an activated intracellular signal transforming domain (amended claim 1).

Finally, the reference of Kasahara, et al., does not make up for the shortcomings of either of the previous two references. The reference of Kasahara, et al., provides a molecular analysis of the *Salmonella typhimurium* phoN gene, which encodes a non-specific acid phosphatase. The reference generally describes the phoQ/phoP transduction system. There is no teaching or suggestion of any modifications that would alter the ligand-specific binding domain of the phoP/phoQ system, for example, modification of

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the phoQ coding sequence to produce a fusion protein comprising an epitope-binding fragment of an antibody such that binding of the target substance to the epitope-binding fragment results in a conformational change in the fusion protein that results in activation of the specific phosphorylase activity which activates phoP.

None of the references cited provides motivation for modifying Contag, et al., and/or Georgiou, et al., to specifically include a signal converting element, comprising (i) an extracellular ligand-specific binding domain which specifically binds the selected substance, wherein the ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain, wherein binding of target substance to the epitope-binding fragment of the ligand-specific binding domain activates the intracellular signal transforming domain, thus providing an activated intracellular signal transforming domain (amended claim 1).

The Examiner suggests the following:

> Since the use of various regulatory promoters (operons) would be known by one of skill in the art, it would have been obvious to said artisan to use the phoP-phoQ operon disclosed by Kasahara et al. and the heterologous scFv disclosed by Georgiou et al. in order to take advantage of the increase in specificity, diversity, and ease of production of the resulting biodetector. Additionally, by varying the scFv, one could easily create a library of biodetectors (see Georgiou, et al.). (Office action, paragraph bridging pages 5-6).

This assertion finds no basis in the cited references. The Examiner relies on the use of prohibited reconstructive hindsight to formulate the present rejection. The Examiner has picked and chosen among the references based on the teachings of the applicants. There is nothing in the cited references to provide a nexus between the different teachings of the cited prior art and the biodetectors of the present invention. Specifically, the reference of Georgiou, et al., as discussed above, does not teach or suggest modification of a signal transduction system (such as, the phoQ/phoP system) to generate a biodetector. The reference of Georgiou, et al., only makes specific reference to phoP/phoQ in the context of producing recombinant bacterial vaccine vectors (see

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paragraph bridging pages 31-32 of the reference). In the embodiment described by Georgiou, et al., nothing more is disclosed than the following:

> Such outer membrane associated antigens are often capable of correct localization in the heterologous Salmonella host and become displayed on the surface. Expression of heterologous O antigens in Gram-negative bacteria generally result in a strong antibody response and therefore is a promising approach for live bacterial vaccine development (Georgiou, et al., page 32, col. 1, lines 2-7).

The reference contains no teaching or suggestion to modify a signal transduction system (such as, the phoQ/phoP system) to generate a biodetector for the detection of a selected substance wherein binding of target substance to the epitope-binding fragment of the ligand-specific binding domain activates the intracellular signal transforming domain, thus providing an activated intracellular signal transforming domain which ultimately produces expression of a reporter gene.

Even if, *in arguendo*, the elements of the present invention were taught in the prior art, the Federal Circuit in *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569, 19 USPQ2d 1241 (Fed. Cir. 1991) stated the following:

> We do not pick and chose among the individual elements of assorted prior art references to recreate the claimed invention, but rather, we look for some teaching or suggestion in the references to support their use in the particular claimed combination.

Prior to the teachings of the present specification, there was no indication in the prior art that one of ordinary skill in the art would choose to create biodetectors wherein binding of target substance to the epitope-binding fragment of the ligand-specific binding domain activates the intracellular signal transforming domain, thus providing an activated intracellular signal transforming domain. In this regard, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Accordingly, no motivation to combine the references, other than

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hindsight reconstruction, has been supplied by the Examiner. No cited reference provides a reason to pursue development of the biodetector constructs of the present invention.

In view of the above arguments and amendments, the applicants submit that the pending claims define an invention patentable over the cited prior art and that the rejections under 35 U.S.C. §103 should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 325-7812.

Respectfully submitted,

Date: 5 June 2001 By: Gary R Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicants

APPENDIX A

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Claims after entry of amendments in the accompanying paper:

1. (Amended) A biodetector for the detection of a selected substance, said biodetector comprising:

(a) a signal converting element, comprising (i) an extracellular ligand-specific binding domain [moiety] which specifically binds said selected substance, wherein said ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain, wherein binding of said substance to said epitope-binding fragment of said ligand-specific binding domain [said extracellular ligand-specific moiety selectively recognizes said selected substance, which recognition] activates said intracellular signal transforming domain providing an activated intracellular signal transforming domain;

(b) a transducer, wherein (i) said transducer has an inactive form and an active form which are distinct from each other, and (ii) [wherein] said activated intracellular signal transforming domain converts said inactive form of said transducer into said active form of said transducer;

(c) a [responsive] transcription control element, wherein expression mediated by said [responsive] transcription control element is activated by said active form of said transducer; and

(d) a reporter gene operatively linked to said [responsive] transcription control element, wherein [the activated responsive] expression of said reporter gene mediated by said transcription control element causes expression of [the reporter gene to generate] a reporter gene product [, resulting in] that provides a detectable signal.

2. (Amended) The biodetector of Claim 1, wherein said detectable signal is detected optically.

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3. (Amended) The biodetector of Claim 2, wherein said [reporter gene product] detectable signal is detectable by means selected from the group consisting of bioluminescence detection, calorimetric reactions and fluorescence detection.

4. (Amended) The biodetector of Claim 3, wherein said [reporter gene product] detectable signal is detectable by bioluminescence detection.

5. (Amended) The biodetector of Claim [3] 1, wherein said reporter gene [is] encodes a luciferase.

6. (Amended) The biodetector of Claim 1, wherein said signal converting element is a fusion protein where the extracellular ligand-specific [moiety] binding domain and the intracellular signal transforming domain are heterologous to one another.

7. (Amended) The biodetector of Claim 1, wherein said intracellular signal transforming [element] domain is derived from a membrane signal transmitter.

8. The biodetector of Claim 7, wherein said membrane signal transmitter is from a bacterial two component regulatory system.

9. The biodetector of Claim 8, wherein said membrane signal transmitter is PhoQ.

10. (Amended) The biodetector of Claim 9, wherein said [responsive] transcription control element comprises the phoN promoter.

11. (Amended) The biodetector of Claim 9, wherein said [extracellular ligand-specific moiety is an antibody or] epitope-binding fragment [thereof] of an antibody is

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selected from the group consisting of a single chain variable fragment (ScFv), a Fab fragment, a $F(ab')_2$ fragment, an epitope-binding fragment of a polyclonal antibody, an epitope-binding fragment of a monoclonal antibody, an epitope-binding fragment of a humanized antibody, an epitope-binding fragment of a chimeric antibody, and an epitope-binding fragment of an anti-idiotypic antibody.

12. (Amended) The biodetector of Claim 11, wherein said [extracellular ligand-specific moiety is] epitope-binding fragment of an antibody comprises a single chain variable fragment (ScFv).

13. The biodetector of Claim 1, wherein said biodetector comprises an intact bacterial cell.

14. The biodetector of Claim 13, wherein said biodetector comprises a Gram-positive bacterial cell.

15. The biodetector of Claim 14, wherein said bacterial cell is selected from the group consisting of *Streptococcus, Staphylococcus, Listeria, Clostridium, Bacillus,* and *Corynebacteria.*

16. The biodetector of Claim 13, wherein said biodetector comprises a Gram-negative bacterial cell.

17. The biodetector of Claim 16, wherein said bacterial cell is selected from the group consisting of *Escherichia, Salmonella, Pseudomonas, Helicobacter, Shigella, Proteus, Bordetella, Neisseria, Haemophilus, Bacteriodes, Vibrio, Brucella, Campylobacter, Klebsiella, and Yersinia.*

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18. (Amended) A library of biodetectors, comprising at least about 1000 biodetectors of claim 13, wherein the extracellular ligand-specific [moiety] binding domain of each of said biodetectors comprises a different antibody fragment.

The following claims have been withdrawn from consideration:

19. An expression vector useful for making a fusion protein for use in a biodetector, comprising

(i) a cloning site for insertion of a DNA fragment encoding an extracellular ligand-specific moiety, and (ii) a first DNA fragment encoding an intracellular signal transforming domain,

wherein said vector is capable of expressing a fusion protein comprising (a) a polypeptide encoded by a DNA sequence inserted at said cloning site, and (b) said intracellular signal transforming domain.

20. The vector of claim 19, wherein the vector further comprises, between said cloning site and said first DNA fragment, a second DNA fragment encoding a membrane anchor.

21. The vector of claim 19, wherein the vector further comprises, upstream of said cloning site, a third DNA fragment encoding an N-terminal leader sequence.

22. The vector of claim 19, wherein the vector further comprises, inserted at the cloning site, a fourth DNA fragment encoding an extracellular ligand-specific moiety.

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23. The vector of claim 22, wherein the extracellular ligand-specific moiety comprises an antibody fragment.

24. The vector of claim 19, wherein the first DNA fragment encodes a polypeptide comprising the cytoplasmic tail of PhoQ.

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APPENDIX B

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What is claimed is:

1. A biodetector for the detection of a selected substance, said biodetector comprising:

(a) a signal converting element, comprising (i) an extracellular ligand-specific binding domain which specifically binds said selected substance, wherein said ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain, wherein binding of said substance to said epitope-binding fragment of said ligand-specific binding domain activates said intracellular signal transforming domain providing an activated intracellular signal transforming domain;

(b) a transducer, wherein (i) said transducer has an inactive form and an active form which are distinct from each other, and (ii) said activated intracellular signal transforming domain converts said inactive form of said transducer into said active form of said transducer;

(c) a transcription control element, wherein expression mediated by said transcription control element is activated by said active form of said transducer; and

(d) a reporter gene operatively linked to said transcription control element, wherein expression of said reporter gene mediated by said transcription control element causes expression of a reporter gene product that provides a detectable signal.

2. The biodetector of Claim 1, wherein said detectable signal is detected optically.

3. The biodetector of Claim 2, wherein said detectable signal is detectable by means selected from the group consisting of bioluminescence detection, calorimetric reactions and fluorescence detection.

4. The biodetector of Claim 3, wherein said detectable signal is detectable by bioluminescence detection.

5. The biodetector of Claim 1, wherein said reporter gene encodes a luciferase.

6. The biodetector of Claim 1, wherein said signal converting element is a fusion protein where the extracellular ligand-specific binding domain and the intracellular signal transforming domain are heterologous to one another.

7. The biodetector of Claim 1, wherein said intracellular signal transforming domain is derived from a membrane signal transmitter.

8. The biodetector of Claim 7, wherein said membrane signal transmitter is from a bacterial two component regulatory system.

9. The biodetector of Claim 8, wherein said membrane signal transmitter is PhoQ.

10. The biodetector of Claim 9, wherein said transcription control element comprises the phoN promoter.

11. The biodetector of Claim 9, wherein said epitope-binding fragment of an antibody is selected from the group consisting of a single chain variable fragment (ScFv), a Fab fragment, a $F(ab')_2$ fragment, an epitope-binding fragment of a polyclonal antibody, an epitope-binding fragment of a monoclonal antibody, an epitope-binding fragment of a humanized antibody, an epitope-binding fragment of a chimeric antibody, and an epitope-binding fragment of an anti-idiotypic antibody.

B2 7 12. The biodetector of Claim 6 11, wherein said epitope-binding fragment of an antibody comprises a single chain variable fragment (ScFv).

13. The biodetector of Claim 1, wherein said biodetector comprises an intact bacterial cell.

14. The biodetector of Claim 13, wherein said biodetector comprises a Gram-positive bacterial cell.

15. The biodetector of Claim 14, wherein said bacterial cell is selected from the group consisting of *Streptococcus, Staphylococcus, Listeria, Clostridium, Bacillus,* and *Corynebacteria.*

16. The biodetector of Claim 13, wherein said biodetector comprises a Gram-negative bacterial cell.

17. The biodetector of Claim 16, wherein said bacterial cell is selected from the group consisting of *Escherichia, Salmonella, Pseudomonas, Helicobacter, Shigella, Proteus, Bordetella, Neisseria, Haemophilus, Bacteriodes, Vibrio, Brucella, Campylobacter, Klebsiella, and Yersinia.*

B3 13 18. A library of biodetectors, comprising at least about 1000 biodetectors of claim 13 8, wherein the extracellular ligand-specific binding domain of each of said biodetectors comprises a different antibody fragment.

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